Principles of Regulatory Drug Analysis

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Author's Preface

My purpose in writing this book was twofold: to expound the thesis that penetrating chemical analysis is a crucial factor in the intelligent enforcement of regulatory drug laws; and to depict the role of law enforcement agencies in the development of the official drug compendia.

The collaborative efforts of many institutions must be enlisted before a modern pharmacopeia can be composed and promulgated. It is essential that close cooperation exist between chemists, microbiologists, pharmacologists, and physicians in academic, industrial, and governmental laboratories. My emphasis upon the endeavors of governmental bodies in establishing standards for drug control is not intended to deprecate the invaluable contributions and interest of collaborators in the other scientific sectors.

Much of this text has been reviewed by members of the U. S. Food and Drug Administration. I am especially grateful for the critical comments offered by Mr. James B. Kottemann, Mr. Joseph Levine, Dr. William W. Wright, and Mr. Jonas Carol. However, I alone am responsible for the statements in the book. None of the statements should be construed to represent the judgments and policies of the FDA or any other official agency.

The text benefited immeasurably from the able editorial ministrations of Miss Helen L. Reynolds, technical editor of the AOAC. She and her associates, Miss Irene E. Hemelt, Mrs. Toby Pick, and Miss Martha G. Simon, were indefatigable in prosecuting the onerous tasks of checking the many quotations from the pharmaceutical literature, collating them with the corresponding sections of the text, and reading the proofs. It is a pleasure for me to acknowledge my indebtedness to them.

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CHAPTER I: Regulatory Drug Analysis and The Law

The Legislative Basis of Regulatory Drug Analysis

Drugs which serve to overcome disease and alleviate pain are a boon to suffering mankind. But when improperly prepared or when misused, these substances may become baleful poisons causing serious personal injury, or inducing irrational or even criminal behavior. For this reason, every civilized community has deemed it necessary to enact restrictive laws governing the production, distribution, and use of potentially dangerous drugs. Modern legislative bodies have also undertaken to protect the public from perpetrators of fraud by forbidding the use of false and misleading representations to market worthless products.

The Food, Drug, and Cosmetic Act passed by the Congress of the Republic of the Philippines in 1963 exemplifies the tenor of recent drug legislation. This Act declares it "the policy of the State to insure a safe supply of quality drugs and to regulate the production, sale, and traffic of the same to protect the health of the people." To accomplish these purposes, the Act charges designated governmental officers with responsibility for enforcing its provisions. Among the actions specifically prohibited by the law are the adulteration and misbranding of drugs and the manufacture, sale, or transfer of any illicit drug.

The officials authorized to administer this Food, Drug, and Cosmetic Act are the Secretary of Health and the Food and Drug Administration of the Republic of the Philippines. They are empowered to collect and analyze samples of drugs and to seize an offending drug and hold it in custody if "the Secretary has probable cause to believe from facts found by him or any officer or employee of the Philippine Food and Drug Administration that a misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading, to the injury or damage of the purchaser or consumer." In addition, "when a violation of any provisions of this Act comes to the knowledge of the Food and Drug Administrator of such character that a criminal prosecution ought to be instituted against the offender, he shall certify the facts to the Secretary of Justice through the Secretary of Health, together with the chemist's report . . . or other documentary evidence on which the charge is based."

However, the duties of the enforcement agency are not restricted to penalizing transgressions. To prevent violations and to promote honesty and fair dealing in the interest of the consumer, the Philippine Food and Drug Administration is authorized: to issue rules and regulations interpreting the general provisions of the drug laws and clearly defining the manner in which it proposes to administer them; to inspect drug estab-

lishments and approve regulations describing acceptable operating procedures; to collect and analyze samples of drugs providing analytical data for the preparation of drug standards; and to recommend standards of identity, purity, and fill of container for drug products.

These provisions of the Philippine Food, Drug, and Cosmetic Act indicate the far-ranging scope of contemporary governmental regulatory functions dealing with medicinals. It is obvious that intelligent enforcement of such drug laws must be based upon a profound knowledge of the chemical, pharmacological, and clinical properties of drugs. Among these indispensable scientific capabilities, accurate and imaginative drug analysis is of crucial importance. Responsibility for effective regulatory drug analysis must rest primarily upon the government, for the law can be administered efficiently only when the enforcing authority is well informed and alert in the execution of its duties.

The law is effectively enforced when an overwhelming majority of the marketed drugs comply with all legal requirements and the number of violative preparations is minimal. To foster a spirit of voluntary compliance in the regulated industries, the governmental agency must adopt unambiguous, realistic standards and regulations and must make clear the need and the scientific justification for its actions. Likewise, academic and industrial drug scientists should strive to appreciate the context of regulatory controls and collaborate in improving the quality of regulatory drug analysis within the framework of its special needs. Such collaboration not only reduces the incidence of violations and legal disputes; it also accelerates the development of superior drug science and improved drug products.

Regulatory Drug Analysis as a Legal Instrument

A multitude of analytical problems are associated with the enforcement of drug legislation. The nature and variety of these problems can best be illustrated by correlating them with specific provisions in typical drug laws, such as the previously cited Philippine Food, Drug, and Cosmetic Act and its antecedents in the diverse drug laws of the United States, especially the Federal Food, Drug, and Cosmetic Act of 1938, as amended.

The first legal problem encountered in considering a drug may be the question: Is the product really a drug? In both the Philippine code and the Federal code of the United States, four categories of drugs are defined: (1) articles recognized in the official pharmacopeias and formularies, (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, (3) articles (other than food) intended to affect the structure or any function of the

body of man or animals, (4) articles intended for use as a component of any articles specified in items (1), (2), and (3).

If the government proposes to charge that an article is misbranded because it is a drug of the first category and is not properly labeled to show that fact, physical and chemical testing will be required to demonstrate its identity with the substance recognized in an official drug compendium. Without such identification the applicability of this and related provisions of the law would be jeopardized. A charge that a drug fails to meet its pharmacopeial requirements will be dismissed if there is an unresolved doubt that the drug is identical with the pharmacopeial substance.

In the definitions of the other three categories of drugs, the key word is "intended". Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease could conceivably include anything and everything. If water from the Dead Sea or powdered mummy wrappings, for instance, were offered as a cure for a disease, they would be drugs by this definition. Therefore, they would be subject to the misbranding and adulteration provisions of the law. In bringing charges against a violative product, however, it might become necessary to cite chemical data to show whether the article is in fact what it purports to be. A quantitative determination of water content, together with proximate analyses for the more plentiful cations and anions, might suffice to characterize Dead Sea water. A satisfactory identification of such exotic materials as mummy wrappings might require an intensive study of the properties which characterize the authentic material.

Even more difficult is the complete analysis of secret nostrums. Most of these mysterious drugs are quack remedies promoted by a campaign of extravagant therapeutic claims. Frequently their sale is so lucrative that the enforcement agency must undergo a bitter struggle in the courts before it succeeds in its efforts to remove them from the market.

In preparing to examine any regulatory sample, the government analyst must be conscious of both the scientific and juridical demands of his official duties. The data he accumulates must be proved not only sound, but also impeccably honest. The conclusions he derives from these findings must be scientifically unquestionable. If it becomes necessary to testify before a judge and jury, his evidence must be so well documented that it will inevitably be accepted as true and compelling.

In addition to these obligations, the analyst examining a secret remedy must undertake to devise an analytical system which is capable of determining the identity and quantity of each of the significant substances in the preparation. The techniques employed may be adapted from any sector of analytical chemistry, physics, and biology. Just as the corroborative testimony of several independent witnesses to a sequence of

events is more convincing than that of a single witness, so consistent results obtained by applying several different techniques are more persuasive than reliance upon a single method. Therefore, as many independent techniques are utilized as seem necessary to present an incontrovertible argument.

The regulatory agency must similarly exercise great care in proving its case beyond any reasonable doubt when criminal charges are brought against the distributors of contaminated drugs which are dangerous to public health. A valuable source of auxiliary information is provided by the inspectors whose scientific findings often serve to guide the course of the laboratory investigations. An actual example may be cited to illustrate these statements.

Several years ago several young girls in a California institution for tubercular patients suddenly developed symptoms of sexual precocity. Investigations ruled out water supply, diet, and several other environmental factors as causative agents. It was then hypothesized that the isoniazid tablets administered daily to these young patients might have become contaminated by a substance which caused the estrogenic response. When dosage with these tablets was discontinued, the symptoms of precocious feminization gradually subsided.

The Food and Drug Administration soon confirmed the suspicion of tablet contamination by employing a sensitive biological test which its pharmacologists had previously developed to assay estrogenic drugs. When fed the suspected tablets, test animals showed a positive estrogenic response, while control isoniazid tablets caused no such effects. However, because of the relatively high concentration of isoniazid in the diet fed to the test animals and the controls, the results of the bioassay might have been vulnerable to challenge. Furthermore, the regulatory officials and chemists of the Food and Drug Administration agreed that it would be most desirable to try to isolate and identify the substance responsible for the estrogenic response.

The most potent estrogenic substances are phenolic compounds, whereas isoniazid is nonacidic. Quantitative extraction of 50 tablets with sodium hydroxide solution was followed by appropriate treatment of the alkaline extracts in immiscible solvent systems to segregate phenols. About 3 mg of a white solid was recovered. When treated with certain chromogenic reagents, small portions of this material failed to produce the colors characteristic of estrone, estradiol, or any of the other naturally occurring estrogens. However, positive results were obtained when several micrograms of the substance were irradiated according to a specific procedure devised by chemists of the Food and Drug Administration to assay drug preparations containing the powerful synthetic estrogen, diethylstilbestrol. When another portion of the original tablets was

analyzed quantitatively for diethylstilbestrol by the irradiation method. the results correlated well with the bioassay values.

The remaining portion of the white solid was then recrystallized. The infrared absorption spectrum of the purified substance in a potassium bromide dispersion disk was identical with that of a similarly prepared diethylstilbestrol disk. In addition, the ultraviolet absorption spectrum and chromatographic properties of the contaminant matched those of diethylstilbestrol. The evidence was scientifically conclusive. Nevertheless, FDA decided to collect further data and to prepare for a court contest because the manufacturer vigorously denied that the product was contaminated. He insisted that the phenolic substance recovered from the tablets was the vanillin used as a flavoring agent and that the government tests were fallacious.

Other confirmatory techniques were considered. Mass spectrography, X-ray crystallography, and nuclear magnetic resonance studies, for example, would have provided confirmatory data about the identity of the solid material extracted from the tablets. But a complete analysis of the product also would have been required to check the behavior of all the other ingredients. However, further laboratory investigation was rendered unnecessary in this case by discoveries made during an inspection of the manufacturing plant.

When FDA inspectors examined the production records they noticed that the contaminated batch of isoniazid tablets was punched immediately after a high-potency granulation of diethylstilbestrol had been processed in the same press. They observed, too, that plant equipment was not maintained in an orderly manner. The presses were not usually cleaned between batches, so that sequential contamination was not merely a possibility but a likelihood.

The inspectors noted records of other diethylstilbestrol tabletings, and they ascertained the identity of the drugs following each in the same press. The FDA field service tracked down specimens of several of these products and collected them for examination. Analysis by the specific irradiation procedure showed that some of these samples, too, were contaminated with significant quantities of diethylstilbestrol. When confronted with such a heavily documented case, the manufacturer withdrew his contentions. He was fined by the courts, and the seized drugs were ordered destroyed. Meanwhile, remedial measures had been instituted in the plant to prevent recurrences of such cross-contamination.

An additional burden, proof of jurisdiction, may be placed upon the regulatory agencies of federal governments. In the United States the jurisdiction of the Federal laws extends only to products which move in interstate commerce or whose ingredients have crossed state lines. Those drugs which have been manufactured and sold within the boundaries

of a single state are subject only to the laws of that state. Before charges of adulteration and misbranding can be brought against a drug in the Federal courts of the United States, evidence must be presented to prove that the product or its components were moved in interstate commerce. A spectrographic analysis for trace elements might be of value to support the contention that a sample of bottled water sold in Oklahoma and alleged to be Dead Sea water must have been transported across state lines. The chemical evidence for establishing jurisdiction may be only inferential, but it must be convincing.

Another juridical problem stems from a multiplicity of regulatory drug statutes. In the United States most of the drugs in interstate commerce are subject to the Federal Food, Drug and Cosmetic Act. However, the sale, barter, or exchange of toxins, antitoxins, therapeutic sera, viruses, and related biological products for human use is controlled by regulations issued under the authority of the Public Health Service Act. Separate legislation gives the U. S. Department of Agriculture similar responsibility for analogous biological products intended for veterinary use. Yet another agency, the Treasury Department, regulates the importation, manufacture, and distribution of opium, coca leaves, marihuana, and their derivatives according to the provisions of the Harrison Narcotic Act and the Marihuana Tax Act of 1937. If a drug is improperly alleged to violate a statute which is not applicable to the article, the complaint must be dismissed by the courts. To support the validity of a charge under a particular statute, the drug must be identified chemically as a member of the class of articles to which that statute applies.

Drug Standards Established by Regulation

Official drug standards provide an objective yardstick for judging whether therapeutic substances are properly constituted. There are two essential components of such standards: appropriate analytical procedures to permit a thorough but not an overelaborated examination; and a set of specifications to define acceptable limits for each property tested. When the analytical methods prescribed in the drug standard are specific, accurate, and precise, they provide a reliable route whereby the manufacturer and the regulatory agency can arrive at the same valid decision about the quality of individual products. Thus, they reduce the area of scientific controversy and help to prevent the introduction of substandard drugs into the market.

To serve as an effective regulatory instrument, the specifications set forth in the standard must be discriminating enough to differentiate unequivocally between good and inferior drugs. A standard is arbitrary and unenforceable if it is so exacting that it rejects excellent drugs which

have been prepared in accordance with the best manufacturing procedures. A standard which is so permissive that it passes unsound drugs is worthless as a regulatory criterion.

Agencies of the U. S. Government are authorized by law to issue regulatory standards providing for the certification of insulin and of all antibiotic drugs for human use (Federal Food, Drug, and Cosmetic Act, Sections 506 and 507, respectively). The Antibiotic Regulations are published in the Federal Register, the official organ of the executive branch of the government. A sample of every batch of antibiotic drugs intended for human use must be submitted to the Food and Drug Administration for laboratory testing, unless the product has been exempted by regulation. If the drug meets the specifications promulgated in the appropriate regulation monograph, it can be certified and is eligible for distribution. Otherwise, it is rejected and cannot be marketed legally in the United States.

The monographs in the Antibiotic Regulations specify acceptable characteristics of identity, strength, quality, and purity. These criteria are correlated with physical, chemical, biological, and microbiological examinations comprising identification tests, safety tests, tests for limiting contaminants, and assay procedures.

Obviously, a comprehensive understanding of antibiotics science and technology is necessary if satisfactory analytical methods are to be devised. An assay value that presumably measures the strength of a single antibiotic substance may be misleading if related active compounds are present. Either such compounds must not interfere in the proposed assay procedure, or the interference must be removed by preliminary treatment. These measures imply prior knowledge about the usual constitution of the drug in commerce and about the properties of the constituents. The assay procedure is applied identically to the drug examined and to a reference standard material. The latter, a purified specimen of the same antibiotic substance, is provided in large uniform batches by the manufacturers and is evaluated and maintained by the Food and Drug Administration.

Tests for limiting contaminants must take into account those substances which may interfere in the assay, as well as those which may be deleterious or otherwise undesirable. The identification tests likewise must be based upon the unique properties which distinguish the antibiotic substance from accompanying impurities. It is only by means of such discriminating methods that the identity, strength, quality, and purity of a drug can be reliably determined.

The task of formulating adequate monographs for the Antibiotic Regulations is an arduous responsibility. Before a new drug can be considered for certification by the Food and Drug Administration, the manufacturer

must submit scientific data providing assurances that the drug is safe and efficacious and that it can be produced uniformly from batch to batch. The tests and specifications designed to control the production of the drug are the point of departure for the monograph. FDA scientists subject these proposals to empirical scrutiny in gauging their usefulness as regulatory tools.

The criteria for judging the suitability of a procedure for regulatory drug analysis may be quite different from those guiding a manufacturer who seeks a control method. The manufacturer is free to select any rapid, convenient method which affords a reliable analysis. Since he knows the composition of all the constituents in his preparation and the conditions to which they are subjected during manufacture, he can ascertain the interference due to the inert ingredients. By applying the selected procedure to a sample blank containing all the ingredients except the one being determined, he may compensate for error and thus achieve an acceptable control determination. An acceptable regulatory method, however, must be both quantitatively accurate and universally applicable to all specimens of the drug preparation without dependence on a particular sample blank.

As a result of their experiments, the FDA scientists may suggest modifications or new procedures to overcome inadequacies in the tests and assays proposed by the manufacturer. The latter may then submit counterproposals which are again studied critically. This collaboration ultimately evolves a monograph which is acceptable to the manufacturer as a realistic standard and to the Food and Drug Administration as an effective regulatory measure.

When a regulation incorporating an antibiotic monograph is published in the Federal Register, the drug becomes eligible for certification. If subsequent laboratory experience shows that the regulation adopted does not assure a product which is safe, efficacious, and uniform, the Food and Drug Administration may suspend certification. It may also take action to modify the regulation by means of appropriate amendments published in the Federal Register, if the manufacturer can demonstrate that these changes will provide the required assurances. Prompt publication of new regulations and amendments continuously provides current official standards for all of the antibiotic drugs eligible for certification and distribution.

Although the procedures adopted for the analysis of dosage forms in the Antibiotic Regulations are more rigorous than the simpler methods which may suffice for production controls, they need not be exhaustive. Specific information about the product is available to the regulatory agency from other sources. The manufacturing formula for each certifiable antibiotic drug must be filed with the Food and Drug Administra-

tion, and every deviation from the formula must be reported. FDA inspectors also have access to the plant records and may observe the manufacturing process itself. Furthermore, the antibiotic substances used in the final preparation must have been previously examined and passed by the Food and Drug Administration before a certificate may issue for the dosage form. For these reasons, the assay and identification tests for the dosage forms of these drugs usually are not completely definitive.

However, where noncertifiable drugs are involved, the situation is far different. In this instance, the enforcement agency has no precise information about the history of the individual product. Only the finished article is available for examination. An official monograph for standardizing an uncertified drug requires much more stringent analytical procedures, especially for the examination of dosage forms. In the assay, simplicity and convenience frequently must be disregarded in attempting to achieve specificity without sacrificing accuracy. A full complement of auxiliary tests often must be added to identify the active ingredient conclusively and to limit the concentrations of undesirable substances whose presence indicates decomposition or the use of contaminated materials in fabricating the product. Such assays and tests are among the features of the best monographs in contemporary pharmacopeias.

Drug Standards in Official Compendia

Most of the modern drug statutes recognize the monographs in a specified pharmacopeia or some other compendium as official drug standards. The Food, Drug, and Cosmetic Acts of both the Philippine Republic and the United States accord such recognition to "the official United States Pharmacopeia, the official National Formulary, and the official Homeopathic Pharmacopeia, or any supplement to any of them". Thus, the standards delineated in these compendia have a legal status equivalent to that of the regulations promulgated by the Food and Drug Administration. It is the purpose of the compendia to set standards for the most significant drugs in current use and for the substances needed for preparing the accepted dosage forms. Therefore, they are not merely manuals of operations. They are authoritative documents of prime importance to regulatory analysis.

United States Pharmacopeia.—In many countries an independent governmental body is designated as a pharmacopeial commission with authority to assemble and publish the official compendium. The pharmacopeias and codexes of the United Kingdom, France, Germany, Austria, and the Scandinavian countries are established in this manner. Several governments have adopted monographs of the International Pharmacopeia, issued under the auspices of the World Health Organization. The

United States Pharmacopeia (USP) is recognized similarly as the official compendium of many countries. The USP is exceptional in that it is issued by a nongovernmental organization. Prepared by the USP Committee of Revision, it is published at 5-year intervals (with interim supplements) by authority of the United States Pharmacopeial Convention, Inc. This body is a private institution including representatives from medical schools, pharmacy schools, medical associations, pharmaceutical and chemical societies, drug manufacturers, and governmental agencies. Newer pharmaceutical products which are therapeutic agents of proved value may be considered by the USP Committee on Scope for inclusion in the forthcoming Pharmacopeia. Subcommittees of the Committee of Revision are then responsible for the development of monographs describing these drugs and providing suitable tests and specifications.

The analytical procedures are culled from all available sources and are usually checked in the laboratories cooperating with the members of the Subcommittee. Some of the methods are validated by formal collaborative studies, and the results are published in scientific journals. However, a majority of the new synthetic organic drugs are patented and are manufactured and distributed only by the patent holder. In framing a monograph for these substances, the Committee of Revision must rely heavily upon the information supplied by the manufacturer.

The USP itself contains no references to the background and development of the tests and methods in the monographs. Experimental data are accumulated and are carefully assessed by the appropriate Subcommittees of the Committee of Revision. Upon approval of the Subcommittee and after ratification by the Committee of Revision, the completed monograph is adopted. When it is included in the official compendium, the product described in the monograph becomes an "official drug".

The monographs are presented in a standard format. The heading, or rubric, of the typical monograph consists of the nomenclature, the official definition, the limits or purity statement, and the official description. The body of the monograph generally contains a solubility statement, tests for identity and purity, an assay, directions for packaging and storing, a statement on commonly available sizes, the therapeutic category, and the usual dose. A typical monograph is shown on page 11.

The limits statement, or purity statement, sets limits on the quantities of the active ingredients in a drug. Conformity with the requirement of the purity statement is based upon the assay included in the monograph. By implication, or by explicit assertion, the purity statement indicates the permissible concentrations of harmless impurities. For example, a monograph for Helium states that "Helium contains not less than 95